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Applicant : HESSE et al. Confirmation No: 6670
Appl. No. : 09/926,491
Filed : March 29, 2002
Title : STEROID COMPOUNDS WITH A C-17-ALKYL SIDE CHAIN
AND AN AROMATIC A-RING FRO USE IN THERAPY

TC/A.U. : 1616
Examiner : B. Badio

Docket No.: : HESS3006/REF
Customer No: : 23364

APPEAL BRIEF UNDER 37 CFR §41.37

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief on appeal is submitted along with the required fee. A petition for a three month extension of time and the appropriate fee is submitted herewith extending the period for filing the brief to September 28, 2004. The brief is timely filed.

Any addition fees necessary for this appeal may be charged against the undersigned's Deposit Account No. 02-0200.

(c)(1)(i). REAL PARTY IN INTEREST

The real party in interest is the Assignee of record, Research Institute for Medicine and Chemistry.

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(c)(1)(ii). RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences with respect to the claimed invention which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal known to appellant, appellant's legal representative or assignee.

(c)(1)(iii). STATUS OF CLAIMS

This application contains 21 claims. Claims 18 and 21 have been canceled from the application.

Claims 1-17, 19 and 20 are pending in the application.

Claims 1-5, 7-13, 17 and 19 stand finally rejected under 35 U.S.C. 102(b) as anticipated by Dolence et al.

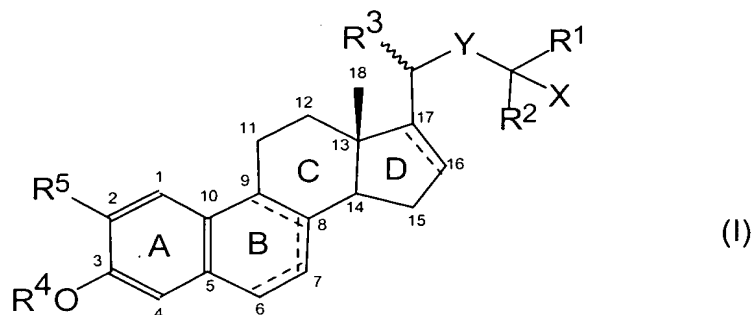
Claims 6, 14-16 and 20 are objected to as dependent on a rejected base claim but are said to contain allowable subject matter.

(c)(1)(iv). STATUS OF AMENDMENTS

No amendment was filed after final rejection.

(c)(1)(v). SUMMARY OF CLAIMED SUBJECT MATTER

Compounds of formula (I)



in which:

R^1 and R^2 , which may be the same or different, each represents a lower alkyl, alkenyl or alkynyl group;

R^3 represents a methyl group having α - or β -configuration;

R^4 represents a hydrogen atom or an etherifying or esterifying group;

R^5 represents a hydrogen atom, a hydroxyl group or a lower alkoxy group;

X represents a group OR^4 , wherein R^4 is as defined above, or a group NR^6R^7 wherein R^6 represents a hydrogen atom, an aliphatic or araliphatic organic group, or an acyl group comprising an aliphatic, araliphatic or aryl organic group linked to the nitrogen atom by way of a carbonyl group; and R^7 is a hydrogen atom or a lower alkyl group;

Y represents a lower alkylene, alkenylene or alkynylene group optionally substituted by a hydroxyl, etherified hydroxyl or esterified hydroxyl group; and

the dotted lines signify that double bonds may be present at the 16(17)-position and/or either at the 6(7)- and 8(9)-positions or at the 7(8)-position. (Page 3, line 25 to page 4, line 22.)

These compounds have cell modulating activity. (Page 7, lines 9 and 10.)

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(c)(1)(vi). GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

Claims 1-5, 7-13, 17 and 19 stand finally rejected under 35 USC § 102(b) as anticipated by Dolence et al. ("A stereoselective synthesis of 1,2-diols from α -hydroxyaldehydes", Tetrahedron Letters, Vol. 26(9), pp. 1189-1192, 1985), and with reference to the abstract of this article from CASREACT, 1985.

(c)(1)(vii). ARGUMENT

A complete copy of Dolence et al. ("A stereoselective synthesis of 1,2-diols from α -hydroxyaldehydes", Tetrahedron Letters, Vol. 26(9), pp. 1189-1192, 1985) article together with copies of two abstracts of the same provided by the Examiner are appended hereto.

It is the Examiner's position that Dolence discloses the compound 3-methoxy-19-norcholesta-1,3,5(10)-triene-22,25-diol, viz. a compound of formula (I) from claim 1 of the instant application in which R^1 and R^2 represent methyl groups, R^3 represents a methyl group having α -configuration, R^4 represents a methyl group, R^5 represents a hydrogen atom, X represents a hydroxyl group and Y represents a hydroxyl-substituted propylene group. This compound is indeed shown in both of the abstracts, as the last compound in the right hand column of Abstract A and as compound Z on page 2 of Abstract B. It is not, however, disclosed in the Dolence article itself, which is concerned exclusively with compounds which additionally carry a hydroxyl group at the 20-position - see in particular the compounds of formulae 6, 7, 8 and 9 on page 1191 of the article.

Thus Dolence is specifically concerned with the conversion of 20R-hydroxypregnane-22-carboxaldehydes to corresponding 20R,22R- or 20R,22S-diols, as is readily apparent from, for example, the initial Abstract, the box on page 1189 and the conversions 5 - 6 - 8 and 5 - 7 - 9 shown on page 1191. When read in this context it is clear that the formula Z in Abstract B and the corresponding

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formula in Abstract A are incorrect and should show a hydroxyl group rather than a hydrogen atom at the 20-position, thereby corresponding to formula 8 on page 1191 of the full article. In this context it will be seen that compound AA of Abstract B corresponds to formula 9 on this page, as does the equivalent compound in Abstract A.

The absence of a 20-hydroxy group in formula Z is also incompatible with the title of the Dolence article, which states that the products are 1,2-diols obtained from α -hydroxyaldehydes. They must therefore carry hydroxyl groups on adjacent side chain carbon atoms, viz. at the 20- and 22-positions in this instance. Moreover, the whole point of the article is the stereoselective synthesis of 20R,22R- or 20R,22S-diols, so that the end products Z and AA in Abstract B must be intended to be stereoisomers of each other.

At the interview with the Examiner on April 24, 2004, when the above points were discussed, the Examiner drew attention to the sentence immediately preceding the box on page 1189 of the Dolence article "This finding provided a convenient solution to the partial synthesis of either the ecdysone or the 22-epiecdysone side chain.". On this basis, and presumably on the basis that ecdysteroids as a general class of compounds are only optionally 20-hydroxylated (see the accompanying extract from the Merck Index), the Examiner maintained that a person of ordinary skill in the art would expect the main reaction product to be a 20,22-diol as in formula AA of Abstract B, accompanied by a small portion of 20-dehydroxylated product as in formula Z. However, as noted above, there is no mention anywhere in the actual Dolence article of 20-dehydroxylated products, so that this cannot be a realistic interpretation of the document. Indeed it is clear from the box which immediately follows the sentence quoted above that the reference to the ecdysone side chain is intended to refer to the 20R,22R-diol threo configuration shown as formula 2t, whilst the 22-epiecdysone side chain must correspond to the equivalent 20R,22S-diol erythro configuration shown as formula 2e.

This logical reading is entirely confirmed by the sentence which begins the last paragraph on page 1190 of the article ("Manipulation of the propargyl alcohols 6 and 7

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provided convenient access to the side chains 8 and 9, respectively, characteristic of the ecdysones and the 22-epiecdysones."). Thus it must inevitably be apparent to one skilled in the art that the terms "ecdysone" and "epiecdysone" as used by Dolence refer exclusively to compounds carrying hydroxyl substituents at the 20R-position and the 22R- or 22S- position, and that the disclosure has no bearing on and permits no inference whatsoever in respect of compounds lacking hydroxyl groups at these positions as would be appreciated from a review of the article which is what would be considered by one of ordinary skill in the art to which the invention pertains.

Moreover, it will be seen that the last paragraph on page 1190 of the article goes on to discuss deprotection conditions which are specifically designed to avoid elimination of hydroxyl groups ("to furnish the desired tertiary alcohols without concomitant elimination"). In light of this stated desire and the actual process conditions used by Dolence to treat intermediates 6 and 7 in order to remove the tetrahydropyranyl protecting group and hydrogenate the acetylenic bond (by treatment with 70% perchloric acid in methanol and catalytic hydrogenation respectively) it is clear to one of ordinary skill in the art to which the invention pertains that Dolence does not in any way envisage the preparation of 20-dehydroxylated products. Indeed, it would be readily apparent to one skilled in the art that no 20-dehydroxylated product was obtained, since Dolence explicitly teaches "we have found that 1:50 70% perchloric acid (9.0 equivalents) in methanol cleanly deprotects tetrahydropyranyl ethers at either C-25, as in 6 and 7 (90% yield) or at C-14 as in 12 (63% yield) to furnish the desired tertiary alcohols without concomitant elimination" (emphasis added).

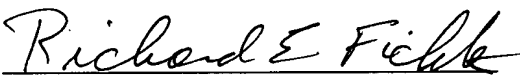
One of ordinary skill in the art, noting that the reaction conditions (perchloric acid/water/methanol followed by hydrogenation) erroneously stated in Abstract B as converting compound R to compound Z are in fact described in the Dolence article as giving the 20R-hydroxy compound 8 corresponding to compound Z in 90% yield without concomitant elimination, would immediately and inevitably recognize the error in formula Z of Abstract B and the corresponding formula in Abstract A.

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For the above reasons the cited compound 3-methoxy-19-norcholesta-1,3,5(10)-triene-22,25-diol is not placed in possession of the public by the Dolence prior art. See *In re Wilder* 166 USPQ 545 (CCPA 1970) wherein the court acknowledged that an applicant claiming a certain compound could avoid the anticipatory effect of a prior reference specifically naming that compound by showing either (1) that the compound "could not possibly have been made by the process taught by the reference," or (2) that the claimed compound has "properties *completely* different from those attributed to them by the reference description.". Accordingly there is no anticipation of the claimed subject matter on appeal and it is respectfully requested that the Examiner's rejection of claim 1-5, 7-13, 17 and 19 be reversed.

Respectfully submitted,

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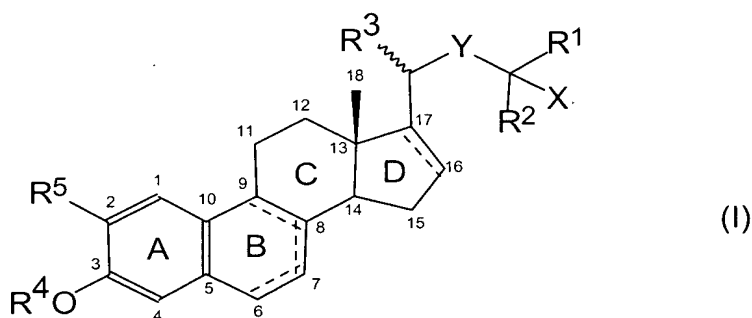
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September 28, 2004

(c)(1)(viii) Claims appendix (A copy of the claims to be reviewed on appeal.)

1. Compounds of formula (I)



in which:

R^1 and R^2 , which may be the same or different, each represents a lower alkyl, alkenyl or alkynyl group;

R^3 represents a methyl group having α - or β -configuration;

R^4 represents a hydrogen atom or an etherifying or esterifying group;

R^5 represents a hydrogen atom, a hydroxyl group or a lower alkoxy group;

X represents a group OR^4 , wherein R^4 is as defined above, or a group NR^6R^7 wherein R^6 represents a hydrogen atom, an aliphatic or araliphatic organic group, or an acyl group comprising an aliphatic, araliphatic or aryl organic group linked to the nitrogen atom by way of a carbonyl group; and R^7 is a hydrogen atom or a lower alkyl group;

Y represents a lower alkylene, alkenylene or alkynylene group optionally substituted by a hydroxyl, etherified hydroxyl or esterified hydroxyl group; and

the dotted lines signify that double bonds may be present at the 16(17)-position and/or either at the 6(7)- and 8(9)-positions or at the 7(8)-position.

2. Compounds of formula (I) as claimed in claim 1 wherein R^1 and R^2 are independently selected from C_{1-6} alkyl groups and C_{2-7} alkynyl and alkynyl groups.

3. Compounds of formula (I) as claimed in claim 2 wherein R^1 and R^2 are straight chain groups.

4. Compounds of formula (I) as claimed in claim 2 wherein R^1 and R^2 are selected from methyl, ethyl and propargyl groups.

5. Compounds of formula (I) as claimed in claim 1 wherein R^4 a hydrogen atom, a silyl group, a C_{1-6} alkyl group optionally interrupted by one or more oxygen atoms or substituted by a lower cycloalkyl group, a cyclic ether group, a C_{1-6} alkanoyl group, an aroyl group, a C_{1-6} alkane sulphonyl or halogenated methane sulphonyl group, or an arene sulphonyl group.

7. Compounds of formula (I) as claimed in claim 5 wherein R^4 is a metabolically labile group or a lower alkyl group.

8. Compounds of formula (I) as claimed in claim 1 wherein R^5 represents a hydrogen atom or a methoxy group.

9. Compounds of formula (I) as claimed in claim 1 wherein X represents a hydroxyl group or a group of formula NR^6R^7 wherein:

R^6 is a C_{1-6} alkyl group, C_{6-12} carbocyclic aryl C_{1-4} alkyl group, C_{1-6} alkanoyl group, C_{6-12} carbocyclic aryl C_{2-5} alkanoyl group, C_{7-13} carbocyclic aroyl group or any of the preceding groups substituted by one or more halo, C_{1-4} alkyl, C_{1-4} alkoxy, C_{1-4} alkanoyl, C_{1-4} alkylamino, di (C_{1-4} alkyl) amino, nitro, carbamoyl or C_{1-4} alkanoylamino substituents; and

R^7 is a hydrogen atom or a C_{1-6} alkyl group.

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10. Compounds of formula (I) as claimed in claim 9 wherein X represents a hydroxyl, amino, methylamino, ethylamino, N-ethyl-N-methylamino, acetylamino, benzamido or phenylacetylamino group.

11. Compounds of formula (I) as claimed in claim 1 wherein Y contains up to 7 carbon atoms and up to 3 multiple bonds.

12. Compounds of formula (I) as claimed in claim 11 wherein Y is a straight chain C₂₋₆ group.

13. Compounds of formula (I) as claimed in claim 1 wherein Y is substituted by a hydroxyl, etherified hydroxyl or esterified hydroxyl group positioned α -, β - or γ - to the group -C(R¹)(R²)[[.]]. X or α - to any triple bond present in the group Y.

17. Active compound of formula (I) as claimed in claim 1 for use in management of neoplastic disease; as agents to promote wound healing; in burn management; in treatment of bone diseases, autoimmune disease, host-graft reaction, transplant rejection, inflammatory diseases, neoplasias or hyperplasias, myopathy, enteropathy or spondylitic heart disease; in suppression of parathyroid hormone; in treatment of dermatological diseases, hypertension, rheumatoid arthritis, psoriatic arthritis, secondary hyperparathyroidism, asthma, cognitive impairment or senile dementia; in fertility control in either human or animal subjects; in management of disorders involving blood clotting; or in reduction of serum cholesterol.

19. Pharmaceutical compositions comprising an active compound of formula (I) as claimed in claim 1 in admixture with one or more physiologically acceptable carriers or excipients.

A STEREoseLECTIVE SYNTHESIS OF 1,2-DIOLS
FROM α -HYDROXYALDEHYDES

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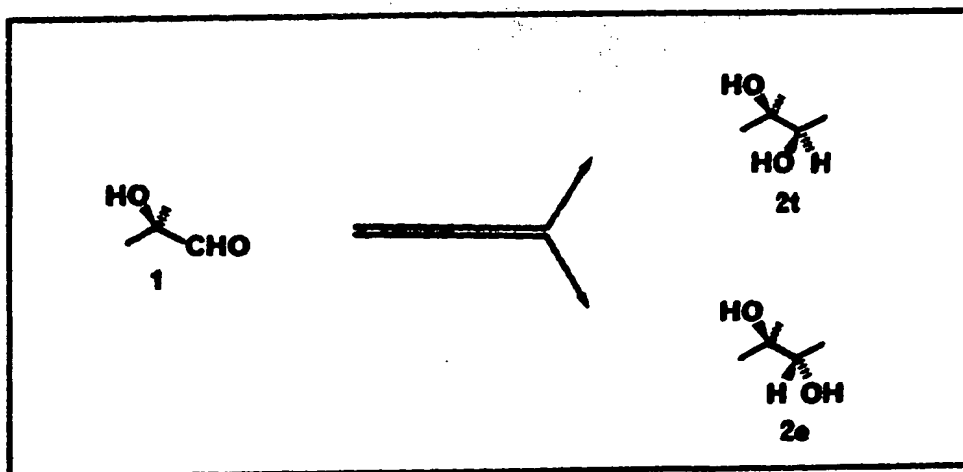
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Abstract. The addition of lithium acetylides to (20R)-20-hydroxypregnane-22-carboxaldehydes in the absence and in the presence of BF₃ afforded predominantly 20R,22R- or 20R,22S-diols, respectively, characteristic of ecdysones.

The addition of nucleophiles to chiral α -hydroxyaldehydes 1 constitutes a valuable procedure for the diastereoselective synthesis of 1,2-diols 2. In connection with our interest in the partial synthesis of ecdysones,¹ we examined the addition of lithium acetylides to (20R)-20-hydroxypregnane-22-carboxaldehydes 5 and observed that certain Lewis acids dramatically altered the stereoselectivity of the addition process. In particular, the addition of boron trifluoride² altered the usual outcome leading to the threo-diastereomer 2t and led instead to the erythro-diastereomer 2e. This finding provided a convenient solution to the partial synthesis of either the ecdysone or the 22-epiecdysone side chain.

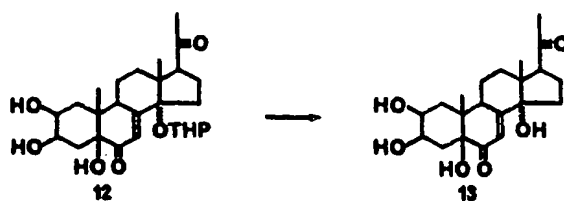


The Darzens condensation of pregnan-20-ones 3 and the subsequent ring opening of epoxysulfones 4 furnished the desired substrates, the α -hydroxyaldehydes³ 5, in a highly stereoselective reaction. As summarized in Table I, the condensation of 5x or 5y with $\text{LiC}\equiv\text{C}(\text{CH}_3)_2\text{OTHP}$ (10) or $\text{BrMgC}\equiv\text{C}(\text{CH}_3)_2\text{OTHP}$ (11) followed the anticipated stereochemical course to give predominantly the 20R,22R-diastereomer⁴ 6. According to Cram's "cyclic" model⁵ or the Felkin model,⁶ the transition state leading preferentially to 6 involves nucleophilic attack on the "chelated" substrate⁷ from the less hindered direction (as indicated by the emboldened arrow).

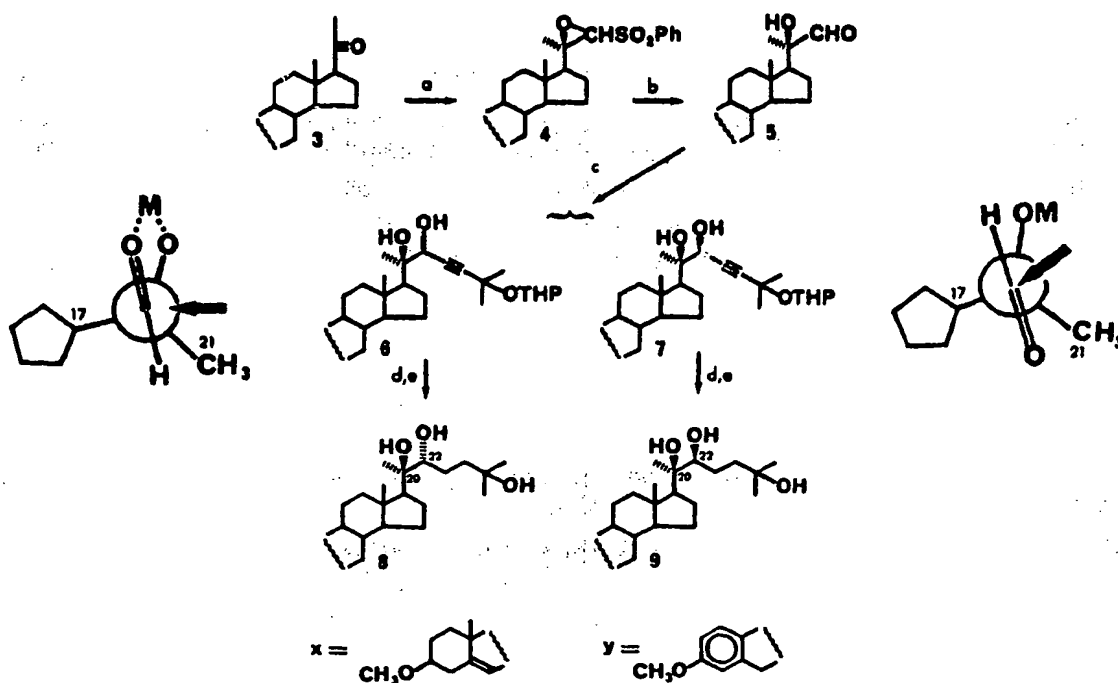
When boron trifluoride was added to the acetylide 10 prior to the addition of 5, this preference for the 20R,22R-diastereomer 6 was inverted and the 20R,22S-diastereomer 7 was the principal product. Independent experiments established that the predominance of 7x was not due to the selective destruction of the epimer 6x or to the epimerisation of 6x during the course of the condensation. Reetz⁸ has recently reported a similar inversion in the reaction of crotyltitanium reagents with simple aldehydes in which a non-cyclic mechanism was suggested to account for erythro-diastereoselectivity in the presence of boron trifluoride. Our own observations involving α -hydroxyaldehydes are also consistent with a non-cyclic mechanism involving either Cram's "dipolar" model or the Felkin model⁶ in which the α -hydroxyaldehyde is transformed to a boron "ate" complex prior to nucleophilic addition. Other Lewis acids ($\text{B}(\text{OCH}_3)_3$, AlCl_3 , etc.) were less effective than boron trifluoride in this particular reaction.

Manipulation of the proparyl alcohols 6 and 7 provided convenient access to the side chains 8 and 9, respectively, characteristic of the ecdysones and the 22-epiecdysones. The stereochemical assignments of these C-22 epimers relied on ^{13}C NMR data (pyridine- d_5) in which the C-22 signal appeared at 77.1-78 ppm for the 22R-epimer and at 76.0-76.8 for the 22S-epimer. In addition, it was important to develop hydrolytic conditions for deprotecting the C-25 tetrahydropyranyl ether that would be compatible with a C-14 α hydroxyl group in a projected synthesis of the natural ecdysones. Standard hydrolytic conditions (PPTS, CH_3OH) fail to remove C-14 α tetrahydropyranyl ether-protected hydroxyl groups,⁹ but we have found that 1:50 70% perchloric acid (9.0 equivalents) in methanol cleanly deprotects tetrahydropyranyl ethers at either C-25, as in 6 and 7 (90% yield) or at C-14 as in 12 (63% yield) to furnish the desired tertiary alcohols without concomitant elimination. Application of this strategy to the partial synthesis of ecdysones will be reported in due course.

Acknowledgement. We thank the National Institutes of Health (CA 30065) and the University of Wyoming (Grant-in-Aid) for their financial support and Professor D. Seebach for helpful discussions.



Scheme I.



a, KOtBu (2.1 eq), ClCH₂SO₂Ph (2.1 eq), 1:2 tBuOH-THF, 72h (3x → 4x in 56% yield; 3y → 4y in 60% yield); b, H₂O (5 eq) in 70.5% KOtBu-tBuOH (15 eq) followed by 1:1 10% HCl-THF, 72h (4x → 5x in 91% yield; 4y → 5y in 95% yield); c, MC≡CC(CH₃)₂OTHP (see Table I); d, 1:50 70% HClO₄/CH₃OH; e, H₂ PtO₂.

Table I.

Substrate	Conditions	Lewis Acid	Isolated Yield (%)	Ratio of 6 to 7
5x	10, THF, -26°C	---	91	2.3:1
5x	11, THF, -26°C	---	76	6.9:1
5y	11, THF, -26°C	---	87	6.9:1
5x	10, THF, -26°C	MgBr ₂	80	6.9:1
5x	10, THF, -26°C	ZnCl ₂	76	2.1:1
5x	10, THF, -26°C	Ti(OiPr) ₄	78	1.5:1
5x	10, THF, -26°C	BF ₃	37	1.0:13
5x	10, THF, -78°C	BF ₃	40	22S only

References

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2. For recent references involving the use of BF₃ in the presence of nucleophiles, see (a) K. Maruyama and Y. Yamamoto, J. Am. Chem. Soc., **99**, 8068 (1977); (b) Y. Yamamoto, S. Yamamoto, H. Yatagai, and K. Maruyama, ibid., **102**, 2318 (1980); (c) A. B. Smith III and P. J. Jerris, ibid., **103**, 194 (1981); (d) M. Suzuki, A. Yanagisawa, and R. Noyori, Tetrahedron Lett., **3595** (1982); (e) A. Pelter and R. Al-Bayati, ibid., **5229** (1982); (f) M. Yamaguchi and I. Hirao, ibid., **391** (1983); (g) M. Yamaguchi, Y. Nobayashi, and I. Hirao, ibid., **5121** (1983); (h) C. N. Meltz and R. A. Volkmann, ibid., **4503** and **4507** (1983); (i) R. A. Volkmann, J. T. Davis, and C. N. Meltz, J. Am. Chem. Soc., **105**, 5946 (1983); (j) A. Ghribi, A. Alexakis, and J. Normant, Tetrahedron Lett., **3075**, **3079** and **3083** (1984); (k) J. Kang, W. Cho, and W. K. Lee, J. Org. Chem., **49**, 1838 (1984); (l) C. H. Heathcock, S. Kiyooka, and T. A. Blumenkopf, ibid., **49**, 4214 (1984).
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4. For analogous condensations in ecdysone syntheses, see (a) G. Huppi and J. B. Siddall, J. Am. Chem. Soc., **89**, 6790 (1967) (5:3 20R, 22R:20R, 22S); (b) H. Mori and K. Shibata, Chem. Pharm. Bull., **17**, 1970 (1969) (high stereospecificity); (c) H. Hikino, T. Okuyama, S. Arihara, Y. Hikino, T. Takemoto, H. Mori, and K. Shibata, ibid., **23**, 1458 (1975) (9:1 20R, 22R:20R, 22S); (d) H. Hikino, K. Mori, Y. Hikino, S. Arihara, T. Takemoto, H. Mori, and K. Shibata, Tetrahedron, **32**, 3015 (1976) (exclusively 20R, 22R).
5. D. J. Cram and K. R. Kopecky, J. Am. Chem. Soc., **81**, 2748 (1959).
6. N. T. Anh and O. Eisenstein, Nouv. J. Chim., **1**, 61 (1977).
7. For recent references to chelation-controlled nucleophilic additions, see W. C. Still and J. H. McDonald III, Tetrahedron Lett., **1031** (1980); (b) W. C. Still and J. A. Schneider, ibid., **1035** (1980).
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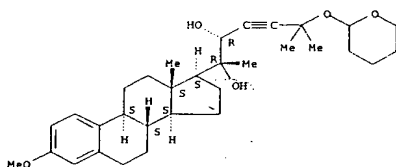
Abstract A

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Page 10

L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS
 ACCESSION NUMBER: 1995:471583 CAPLUS
 DOCUMENT NUMBER: 103:71583
 TITLE: A stereoselective synthesis of 1,2-diols from
 .alpha.-hydroxyaldehydes
 AUTHOR(S): Solence, E. Kurt; Adamczyk, Maciej; Watt, David S.;
 Russell, Graeme B.; Horn, Dennis H. S.
 CORPORATE SOURCE: Dep. Chem., Univ. Wyoming, Laramie, WY, 82071, USA
 SOURCE: Tetrahedron Letters (1995), 26(9), 1189-92
 CODEN: TELEAY; ISSN: 0040-4039
 DOCUMENT TYPE: Journal
 LANGUAGE: English
 OTHER SOURCE(S): CASREACT 103:71583
 AB The addn. of LiC.tplbond.CCMe2O-THP (THP = tetrahydro-2H-pyran-2-yl) to
 (20R)-20-hydroxypregnane-20-carboxaldehydes I and II in the absence and in
 the presence of BF3 afforded predominantly 20R,22R-diols III and IV or
 20R,22S-diols V and VI, resp., characteristic of ecdysones.
 IT 97452-83-0P 97452-84-1P
 RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)
 (prepn. and hydrolysis-hydrogenation of)
 RN 97452-83-0 CAPLUS
 CN 19-Norcholesta-1,3,5(10)-trien-23-yne-20,22-diol, 3-methoxy-25-
 [(tetrahydro-2H-pyran-2-yl)oxy]-, (22R)- (9CI) (CA INDEX NAME)

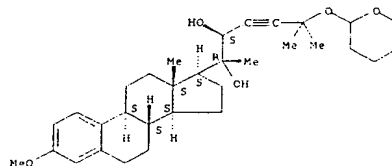
Absolute stereochemistry.



RN 97452-84-1 CAPLUS
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 [(tetrahydro-2H-pyran-2-yl)oxy]-, (22S)- (9CI) (CA INDEX NAME)

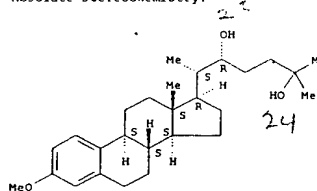
Absolute stereochemistry.

L4 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2003 ACS (Continued)



IT 97452-85-2P 97452-86-3P
 RL: SPN (Synthetic preparation); PREP (Preparation)
 (prepn. of)
 RN 97452-85-2 CAPLUS
 CN 19-Norcholesta-1,3,5(10)-trien-22,25-diol, 3-methoxy-, (22R)- (9CI) (CA
 INDEX NAME)

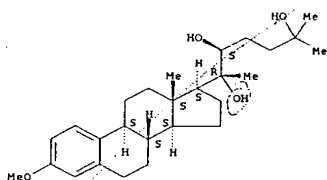
Absolute stereochemistry.



RN 97452-86-3 CAPLUS
 CN 19-Norcholesta-1,3,5(10)-trien-20,22,25-triol, 3-methoxy-, (22S)- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.

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ACCESSION NUMBER: 103:71583 CASREACT

TITLE: A stereoselective synthesis of 1,2-diols from
.alpha.-hydroxyaldehydesAUTHOR(S): Dolence, E. Kurt; Adamczyk, Maciej; Watt, David S.;
Russell, Graeme B.; Horn, Dennis H. S.

CORPORATE SOURCE: Dep. Chem., Univ. Wyoming, Laramie, WY, 82071, USA

SOURCE: Tetrahedron Letters (1985), 26(9), 1189-92

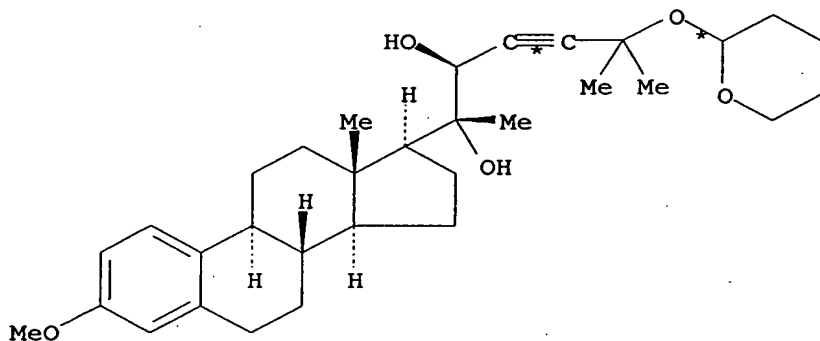
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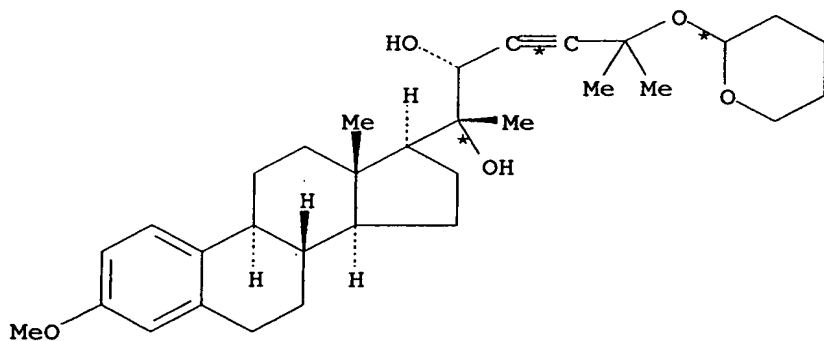
LANGUAGE: English

AB The addn. of LiC.tplbond.CCMe20-THP (THP = tetrahydro-2H-pyran-2-yl) to (20R)-20-hydroxypregnane-20-carboxaldehydes I and II in the absence and in the presence of BF₃ afforded predominantly 20R,22R-diols III and IV or 20R,22S-diols V and VI, resp., characteristic of ecdysones.

RX(9) OF 53 ...R + Q ==> Z + AA

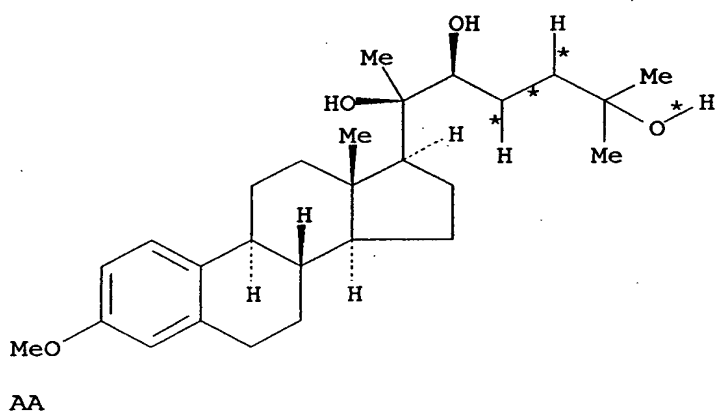
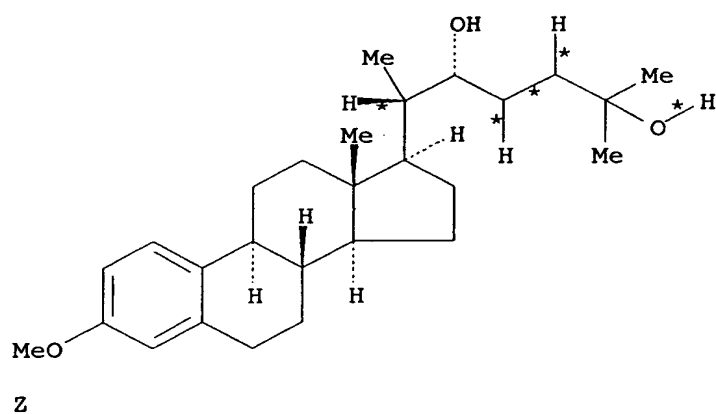


R



Q

(9) →



RX(9) RCT R 97452-84-1, Q 97452-83-0

STAGE(1)

RGT U 7601-90-3 HClO₄

SOL 7732-18-5 Water, 67-56-1 MeOH

STAGE(2)

RGT V 1333-74-0 H₂

CAT 1314-15-4 PtO₂

PRO Z 97452-85-2, AA 97452-86-3

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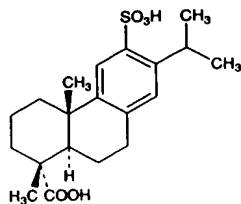
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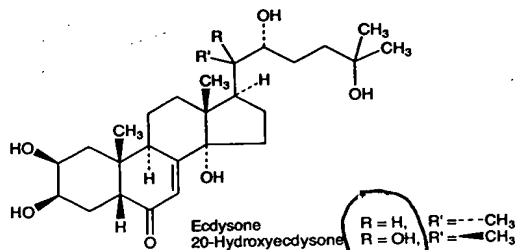
533 (1991). Efficacy in healing expt ulcers in rats: Y. Onoda *et al.*, *Arzneimittel-Forsch.* **41**, 546 (1991). Gastro-protective effects in rats in comparison with sucralfate, q.v.: M. Kinoshita *et al.*, *Digest. Dis. Sci.* **40**, 661 (1995). Bactericidal activity against *Helicobacter pylori*: K. Shibata *et al.*, *Antimicrob. Ag. Chemother.* **39**, 1295 (1995).



As the hemihydrate, $[\alpha]_D^{25} +72.4$ ($c = 2.5$ in alcohol). Sodium salt, $C_{20}H_{27}NaO_5S$, (+)-(1*R*,4*S*,10*aR*)-1,2,3,4,5*a*-,9,10,10*a*-octahydro-1,4*a*-dimethyl-7-(1-methylethyl)-6-sulfo-1-phenanthrenecarboxylic acid 6-sodium salt, TA-2711, *Gastron.* Occurs as pentahydrate, mp $> 300^\circ$. $[\alpha]_D^{25} +59.4^\circ$ ($c = 0.5$).

THERAP CAT: Antilcerative.

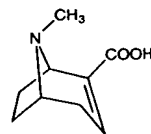
3539. Ecdysteroids. Polyhydroxylated steroids formerly known as ecdysones. Originally identified as insect molting hormones controlling the pupation of insects. Later shown to be involved in many complex developmental processes in metamorphosis, differentiation and reproduction. Ecdysteroids have been detected in invertebrate species of several phyla belonging to the Protostomia and in some plant species. The terms *zooeecdysteroids* and *phytoecdysteroids* are used to distinguish ecdysteroids isolated from animal species from those of plant origin. Nomenclature: T. W. Goodwin *et al.*, *Nature* **272**, 122 (1978). The two major ecdysteroids isolated are ecdysone and 20-hydroxyecdysone. Configuration: M. Koreeda *et al.*, *J. Am. Chem. Soc.* **93**, 4084 (1971). Chromosomal action: M. Ashburner, *Nature* **285**, 435 (1980). GC and HPLC determ: R. P. Evershed *et al.*, *J. Chromatog.* **390**, 357 (1987). Reviews: Kilby, *Discovery* **18**, 13 (1957); P. Karlson, *Angew. Chem. Int. Ed.* **2**, 175-182 (1963); K. Nakanishi, *Pure Appl. Chem.* **25**, 167-195 (1971); M. Koreeda, B. A. Teicher, *Anal. Biochem. Insects* **1977**, 207-240; P. Karlson, *Dev. Endocrinol.* **7**, 1-11 (1980). Book: *Ecdysone: From Chemistry to Mode of Action*, J. Koolman, Ed. (Thieme, New York, 1989) 482 pp.



Ecdysone. $C_{27}H_{44}O_6$, (2*B*,3*B*,5*B*,22*R*)-2,3,14,22,25-Pentahydroxycholest-7-en-6-one, α -ecdysone. Secreted by ecdysial tissues, then transformed to more active compound, 20-hydroxyecdysone. First isoln from silkworm moths, *Bombyx mori*: A. Butenandt, P. Karlson, *Z. Naturforsch.* **9b**, 389 (1954). Isoln from rhizomes of *Polypodium vulgare* L.: G. Heinrich, H. Hoffmeister, *Experientia* **23**, 995 (1967); from bracken fern, *Pteridium aquilinum*: J. N. Kaplanis *et al.*, *Science* **157**, 1436 (1967). Structure: P. Karlson *et al.*, *Ber.* **98**, 2394 (1965). Configuration: R. Huber, W. Hoppe, *ibid.* **2403**. Synthesis: U. Kerb *et al.*, *Helv. Chim. Acta* **49**, 1601 (1966); J. B. Siddall *et al.*, *J. Am. Chem. Soc.* **88**, 379, 862 (1966); H. Mori *et al.*, *Chem. Pharm. Bull.* **16**, 563 (1968). mp 238-239°. $[\alpha]_D^{25} +62^\circ$. uv max: 243 nm (ϵ 11600).
20-Hydroxyecdysone. $C_{27}H_{44}O_7$, (2*B*,3*B*,5*B*,22*R*)-2,3,14-,20,22,25-Hexahydroxycholest-7-en-6-one, β -ecdysone, ecdysterone, crustecdysone, isoinokosterone, polypodine A. Most

widely occurring ecdysteroid in both plant and animal species. Isoln from *B. mori*: P. Hocks, R. Wiechert, *Tetrahedron Letters* **1966**, 2989; from seawater crayfish, *Jasus lalandei*: F. Hampshire, D. H. S. Horn, *Chem. Commun.* **1966**, 37. Isolns from plant sources, *Achyranthes fauriei*: T. Take-moto *et al.*, *Yakugaku Zasshi* **87**, 325 (1967); *P. elatus*: M. N. Galbraith, D. H. S. Horn, *Chem. Commun.* **1966**, 905; *P. vulgare*: J. Jizba *et al.*, *Tetrahedron Letters* **1967**, 1689. Isoln from parasitic helminths: H. H. Rees, J. G. Mercer, *Adv. Invertebr. Reprod.* **4**, 173 (1986). Configuration: Dam-meier, Hoppe, *Ber.* **104**, 1660 (1971). Synthesis: G. Hüppi, J. B. Siddall, *J. Am. Chem. Soc.* **89**, 6790 (1967); U. Kerb *et al.*, *Tetrahedron Letters* **1968**, 4277; H. Mori, K. Shibata, *Chem. Pharm. Bull.* **17**, 1970 (1969). Total synthesis: T. Kametani *et al.*, *Tetrahedron Letters* **21**, 4855 (1980). From methanol-ethyl acetate, mp 240-242°. uv max: 243 nm (ϵ 10300). Unstable in alkaline soln.

3540. Ecgonidine. (1*R*)-8-Methyl-8-azabicyclo[3.2.1]-oct-2-ene-2-carboxylic acid; 2-tropidinecarboxylic acid; anhydroecgonin. $C_9H_{13}NO_3$; mol wt 167.21. C 64.65%, H 7.84%, N 8.38%, O 19.14%. Prepn from ecgonine and structure: Findlay, *J. Am. Chem. Soc.* **75**, 1033 (1953). Prepn and formation of l-form: de Jong, *Rec. Trav. Chim.* **42**, 980 (1923), **66**, 99 (1947). Synthesis of dl-form: Grundmann, Ottmann, *Ann.* **605**, 24 (1957); U.S. pat. 2,783,235 (1957 to Olin Mathieson).

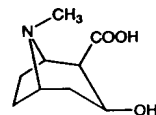


dl-Form, crystals from alcohol + ether, dec 235-236°. Soluble in water; sparingly sol in alcohol.

l-Form, crystals from abs alcohol, mp 235°. $[\alpha]_D^{25} -84.6^\circ$ ($c = 1.7$).

THERAP CAT: Anesthetic (topical).

3541. Ecgonine. [(1*R*-(exo,exo))-3-Hydroxy-8-methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid; 3*B*-hydroxy-1*aH*-,5*aH*-tropene-2*B*-carboxylic acid. $C_9H_{13}NO_3$; mol wt 185.22. C 58.36%, H 8.16%, N 7.56%, O 25.91%. The principal part of the cocaine molecule; naturally occurring as the l-form. Obtained by hydrolysis of cocaine: Willstätter *et al.*, *Ann.* **434**, 111 (1923); Bell, Archer, *J. Am. Chem. Soc.* **82**, 4642 (1960). From coca leaves: de Jong, *Rec. Trav. Chim.* **59**, 687 (1940). Structure: Gadamer, John, *Arch. Pharm.* **259**, 227 (1921). Stereochemistry: Fodor, *Nature* **170**, 278 (1952); Fodor, Kovács, *J. Chem. Soc.* **1953**, 724. Synthesis: Willstätter, Bommer, *Ann.* **422**, 15 (1920). Review: Stoll, Jucker, *Angew. Chem.* **66**, 376 (1954).



l-Form monohydrate, triboluminescent, monoclinic prisms from alc, mp 198° (anhydr, dec 205°). $[\alpha]_D^{25} -45^\circ$ ($c = 5$). Neutral to litmus. pKa 11.11; pKb 11.22. One gram dissolves in 5 ml water, 67 ml alc, 20 ml methanol, 75 ml ethyl acetate. Sparingly sol in acetone, ether, benzene, chloroform, petr ether.

Hydrochloride, $C_9H_{13}NO_3 \cdot HCl$, triclinic plates from water, mp 246°. $[\alpha]_D^{25} -59^\circ$ ($c = 10$). Sol in water; slightly in alc.

dl-Form trihydrate, plates from 90% alcohol, mp 93-118° (anhydr dec 212°).

Note: This is a controlled substance listed in the U.S. Code of Federal Regulations, Title 21 Part 1308.12 (1995).

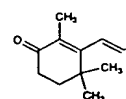
THERAP CAT: Anesthetic (topical).

3542. Echinacea. Cone flower. Dried rhizome and roots of *Echinacea pallida* (Nutt.) Britt. or *E. angustifolia* DC. (*Brauneria pallida* Nutt.) Britt., *Compositae*. Habit.

Saskatchewan sucrose, betain echinacein (neo acid glycoside). *Acta* **33**, 1877. Crombie, Tayl

Note: A com has been used Koch, Haase, *ibid.* **5**, 320 (19

3543. Ech tene; 4-keto- β - mol wt 550.87. pigment occur aqua: Tischer, (1939); from *P* **201, 300 (193; Lythgoc, *J. Ch Taha, Biochem. ibid.* **63**, 481 (1 **60**, 345 (1956). **1958**, 3986; 19**



Orange-red c 180°. Absorpti sol in carbon d pyridine, ether. A activity 54%. Oxime, $C_{40}H$ Absorption ma

3544. Ech oxy-1,4-naphthi 1,4-naphthoquin H 3.79%, O 42. urchin (*Arbacia Wallenfels, Ber.* **1, 3,4-trimetho dride: Wallenf**

Deep-red nee compn). Subli (chloroform): water, yet more Readily sol in concd H_2SO_4 .

3545. Echi mol wt 1101.27 S 5.82%. A "q q.v.: Kuroya, l ful, selective ind duced by *Strept gola*: Corbaz Structure: Kell vised structure: (1975); D. G. Identity with q Ag. Chemother. *J. Biochem.* **7, 1 quinomycins: (1961); Otsuka, *dron* **23**, 1535 (et al., *J. Am. C***

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